(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 285 209 B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: 05.05.93

(51) Int. Cl.[5]: A01N 37/34, A01N 37/30, A01N 25/10, C02F 1/50

(21) Application number: 88200525.9

(22) Date of filing: 22.03.88

(54) **Sustained release microbiological control composition and method for biological control using said composition.**

(30) Priority: 23.03.87 US 29017

(43) Date of publication of application: 05.10.88 Bulletin 88/40

(45) Publication of the grant of the patent: 05.05.93 Bulletin 93/18

(84) Designated Contracting States: AT BE CH DE ES FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 145 846
CA-A- 1 180 852
US-A- 3 865 724
US-A- 4 285 765

(73) Proprietor: THE DOW CHEMICAL COMPANY
2030 Dow Center Abbott Road P.O. Box 1967
Midland Michigan 48640-1967(US)

(72) Inventor: Karbowski, Robert J.
555 Saxton
Sanford, MI 48657(US)
Inventor: Gartner, Charles D.
2400 Burlington
Midland, MI 48640(US)
Inventor: Erickson, Anita S.
2608 St. Marys Drive
Midland, MI 48640(US)
Inventor: Roy, Kathleen A.
1509 Summit Place Drive
Dunwoody, GA 30338(US)

(74) Representative: Smulders, Theodorus A.H.J., Ir. et al
Vereenigde Octrooibureaux Nieuwe Parklaan 97
NL-2587 BN 's-Gravenhage (NL)

EP 0 285 209 B1

Description

This invention relates to solid, non-medicinal, sustained release, antimicrobial compositions which comprise a halogenated amide as the active (i.e., antimicrobial) ingredient and a suitable hydrophilic polymer.

Halogenated amides such as 2,2-dibromo-3-nitrilopropionamide (DBNPA) are well-known antimicrobials useful in a variety of antimicrobial applications.

Halogenated amides are known to rapidly degrade under use conditions and this rapid degradation is a beneficial environmental feature; however, the rapid degradation is a severe detriment when biocidal persistence is desired or necessary.

Although it has long been desired in the antimicrobial field to have a composition and/or method to increase the persistence of halogenated amide antimicrobials, heretofore such compositions and/or methods have not been available. The present invention provides for a means of meeting the long felt need in the art by use of compositions containing halogenated amide antimicrobials and hydrophilic polymers.

Polymers suitable for use in the present invention, such as natural and synthetic hydrophilic cellulosic polymers, are known. However, use of such polymers with halogenated amide antimicrobials to obtain solid compositions of increased biocidal persistence has been heretofore unknown. The method of the present invention provides for an unexpected increase in antimicrobial efficiency relative to current state of the art methods of use.

The present invention provides solid, non-medicinal, antimicrobial composition providing for sustained release of the active ingredient (i.e., the halogenated amide) when used in industrial aqueous systems. More specifically, the present invention provides a solid antimicrobial composition comprising:

(a) 1 to 90 percent by weight of a halogenated amide antimicrobial compound of the formula,

$$R^1-\underset{X}{\overset{Br}{\underset{|}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}-N-(R)_2$$

wherein

x is hydrogen, halogen or a cyano radical;

each R group is independently hydrogen, a monovalent saturated hydrocarbon radical or an inertly substituted monovalent saturated hydrocarbon radical or the two R groups are, jointly, a divalent saturated hydrocarbon radical, or an inertly substituted divalent saturated hydrocarbon radical, which, taken with the adjacent nitrogen atom, forms a heterocyclic ring having from 4 to 10 ring members; and

R^1 is a cyano radical or an amido radical having the formula:

$$-\overset{O}{\overset{\|}{C}}-N\!\left(R^2\right)_2$$

wherein R^2 has the same meaning as R;

(b) 10 to 80 percent by weight of a suitable hydrophilic polymer which is a natural water soluble cellulosic polymer, a synthetic water soluble cellulosic polymer, gelatin, maltodextrin, xanthan gum, carrageenan, carboxymethyl guar, hydroxypropyl guar, carboxymethyl galactomannose or Polyvinylpyrrolidone;

(c) 0 to 80 percent by weight of a compression agent; and

(d) 0 to 10 percent by weight of a mold release agent.

EP-A-0,145,846 describes a controlled release composition comprising:

(a) 2-50 percent by weight of a biologically active agent,

(b) 5-95 percent by weight of a (water soluble) polyhydroxy polymer, which may be dextrin, methyl cellulose or hydroxypropyl cellulose; and

(c) 5-90 percent by weight of an inorganic salt. However, the antimicrobial compound as used in accordance with the present invention is not disclosed, nor suggested in said document.

The present invention also provides to a method for biological control in an aqueous industrial system in need of such control comprising contacting the system with an antimicrobially effective amount of the solid antimicrobial composition.

The terms "antimicrobial compound" and "halogenated amide antimicrobial" are used interchangeably herein and refer to halogenated amides which function as biocides (i.e., compounds which inhibit the growth of, or kill, microorganisms such as, for example, bacteria, molds, yeasts, algae and protozoa).

The term "effective amount" refers to that amount of the solid antimicrobial composition of the present invention that provides for biological control in an aqueous industrial system. The term "biological control" or "biologically controlling" refers to prevention, reduction, or elimination of any adverse consequences such as slime formation, corrosion, odor production, etc., in aqueous industrial systems that are directly, indirectly, or otherwise due to the presence and/or growth of microorganisms.

Those aqueous industrial systems contemplated for application of the method of the present invention are those aqueous industrial systems susceptible to the growth or presence of microorganisms; for example, cooling towers, pulp and paper mills, metalworking fluids, and air washers.

The solid antimicrobial compositions of the present invention and the method of using thereof provide for, inter alia, the following advantages:

1). Persistence of the rapidly degrading halogenated amide compound while in a closed system,

2). Continuous applications to an aqueous industrial system by non-mechanical means without the use of pumps (i.e., an eductor or a similar dispersing apparatus),

3). Relatively constant concentrations of the antimicrobial compound in spite of water turnover in the system,

4). Ease of treatment relative to manual introduction of liquids, and

5). An unexpected improvement in biocidal efficiency relative to the currently practiced application methods.

Halogenated amide antimicrobials employed in the practice of this invention are alpha-haloamides, that is, compounds which contain an amide functionality (i.e., a moiety of the formula -C(O)-N<) and which have at least one halogen atom on a carbon atom located adjacent to (i.e., in the alpha position relative to) the carbonyl group (i.e., the -C(O)- group) of such amide functionality. As mentioned above, the halogenated amide antimicrobials used in the composition of the present invention are halogenated nitrilopropionamides or halogenated malonic diamides having the formula:

$$R^1-\overset{Br}{\underset{X}{C}}-\overset{O}{\overset{\|}{C}}-N-(R)_2$$

wherein

X is hydrogen, halogen or a cyano radical,

i.e., -C≡N, (preferably hydrogen, chlorine or bromine);

each R group is independently hydrogen, a monovalent "saturated hydrocarbon radical" or an inertly substituted monovalent "saturated hydrocarbon radical" or the two R groups are, jointly, a divalent "saturated hydrocarbon radical", or an inertly substituted divalent "saturated hydrocarbon radical", which, taken with the adjacent nitrogen atom, forms a heterocyclic ring having from 4 to 10 ring members: and

R^1 is a cyano radical (i.e., -C≡N) or an amido radical having the formula:

$$-\overset{O}{\overset{\|}{C}}-N(R^2)_2$$

wherein R^2 has the same meaning as R. (Preferably R^1 is a cyano radical).

As used herein, the term "saturated hydrocarbon radical" refers to a hydrocarbon radical which is free of aliphatic carbon to carbon unsaturation. Thus, such term includes radicals such as, for example, alkyl, cycloalkyl, aryl, alkylaryl, arylalkyl and cycloalkylaryl and excludes radicals such as alkenyl, cycloalkenyl

and alkynyl.

As used herein, the term "inertly substituted saturated hydrocarbon radical" refers to a "saturated hydrocarbon radical" having one or more chain linkage or substituent which is "inert" in the sense that such chain linkage or substituent does not readily react with the ingredients of the antimicrobial composition. Suitable inertly substituted saturated hydrocarbon radicals thus include, for example, haloalkyl, haloaryl, halocycloalkyl, aminoalkyl, aminoaryl, aminocycloalkyl, hydroxyalkyl, hydroxyaryl, hydroxycycloalkyl, cyanoalkyl, cyanoaryl and cyanocycloalkyl.

The aforementioned halogenated amide antimicrobials of the formula I thus include brominated nitrilopropionamides (i.e., compounds of the formula I wherein R^1 is a cyano radical), such as, for example, 2-bromo-3-nitrilopropionamide, 2-bromo-2,3-dinitrilopropionamide, 2,2-dibromo-3-nitrilopropionamide, N-(n-butyl)-2-bromo-3-nitrilopropionamide; N,N-dimethyl-2,2-dibromo-3-nitrilopropionamide, 2-chloro-2-bromo-3-nitrilopropionamide, N-(n-propyl)-2-iodo-2-bromo-3-nitrilopropionamide, N-methyl-N-ethyl-2-fluoro-2-bromo-3-nitrilopropionamide, N-phenyl-2-cyano-2-bromo-3-nitrilopropionamide, N-cyclohexyl-2,2-dibromo-3-nitrilopropionamide, N-benzyl-2-bromo-3-nitrilopropionamide, and N-(2,2-dibromo-3-nitrilopropionoyl)-piperidine.

The aforementioned halogenated amide antimicrobials of the formula I also include mono- and di-bromomalonic diamides (i.e., compounds of the formula I wherein R^1 is an amido radical as hereinbefore described), such as, for example, 2-bromomalonic diamide, 2,2-dibromomalonic diamide, N-methyl-N'-ethyl-2-chloro-2-bromomalonic diamide and N-phenyl-2-iodo-2-bromomalonic diamide.

Among the halogenated amide antimicrobials, those wherein, in the formula I, R^1 is a cyano radical, X is hydrogen, chlorine or bromine and each R is independently hydrogen, lower alkyl (i.e., an alkyl group of from 1 to 6 carbon atoms) or phenyl are preferred, especially those of the formula I wherein each R independently is hydrogen or methyl and X is hydrogen or bromine. Such halogenated amide antimicrobials include 2-bromo-3-nitrilopropionamide, 2,2-dibromo-3-nitrilopropionamide, N-methyl-2-bromo-3-nitrilopropionamide, N-phenyl-2-bromo-2-chloro-3-nitrilopropionamide, N-methyl-2,2-dibromo-3-nitrilopropionamide, N,N-dimethyl-2-bromo-3-nitrilopropionamide, N,N-diethyl-2,2-dibromo-3-nitrilopropionamide, and N,N-dimethyl-2,2-dibromo-3-nitrilopropionamide.

Also of particular interest are the dibrominated nitrilopropionamides (i.e., the halogenated amide antimicrobials of the formula I wherein X is bromine and R_1 is cyano) wherein each R independently is hydrogen, lower alkyl (i.e., containing from 1 to 6 carbon atoms) or phenyl. Such compounds include, for example, 2,2-dibromo-3-nitrilopropionamide, N-(n-butyl)-2,2-dibromo-3-nitrilopropionamide, N,N-dimethyl-2,2-dibromo-3-nitrilopropionamide and N-phenyl-N-methyl-2,2-dibromo-3-nitrilopropionamide; especially 2,2-dibromo-3-nitrilopropionamide.

The suitable hydrophilic polymers useful in the solid composition of the present invention include natural and synthetic water soluble cellulosic polymers such as methyl cellulose and hydroxypropyl methyl cellulose.

Also suitable are natural hydrophilic polymers such as, for example, gelatin, maltodextrin, xanthan gum and carrageenan: and synthetic hydrophilic polymers such as, for example, carboxymethyl guar, hydroxypropyl guar, carboxymethyl galactomannose and polyvinylpyrrolidone. It is contemplated that mixtures of suitable hydrophilic polymers are within the scope of the present invention.

The following are some examples of commercially available polymers that are suitable for use in the solid composition of the present invention: Methocel® A15LV, Methocel® A4C, Methocel® A15C and Methocel® A4M, Methocel® K 35LV, Methocel® K15MP, Methocel® K100 MP, Methocel® K 100LV, Methocel® K 4M, Methocel® K 15M, Methocel® E 5, Methocel® E 15LV, Methocel® E50, Methocel® E4M, Methocel® F50, and Methocel® F4M.

The solid compositions of the present invention may also optionally contain a mold release agent. The particular mold release agent used is not critical and can be any suitable mold release agent known in the art that is compatible with the other ingredients. Examples of suitable mold release agents include acid lubricants such as adipic acid, fumaric acid, and stearic acid: polymeric lubricants such as polyfluorocarbon lubricants and polyethylene glycol lubricants; and oils such as encapsulated lubricant oils and encapsulated oil-siloxane polymer mixtures.

The solid compositions of the present invention may optionally contain a compression agent. The particular compression agent used is not critical and can be any suitable compression agent known in the art that is compatible with the other ingredients. Examples of suitable compression agents include dicalcium phosphate dihydrate, lactose, sodium phosphate and calcium sulfate dihydrate. Lactose is commercially available in several grades and/or forms which are suitable for use in the present invention; however, for larger tablets, spray-dried lactose is preferred.

The amount of antimicrobial compound in the solid compositions of the present invention is between 1 and 90 percent by weight of the ultimate formulation; a preferred amount is between 10 and 50 percent; and a most preferred amount is between 30 and 50 percent. The amount of hydrophilic polymer in the solid composition of the present invention is between 10 and 60 percent by weight of the ultimate formulation; a preferred amount is between 20 and 50 percent: and a most preferred amount is between 20 and 40 percent. The amount of compression agent in the solid compositions of the present invention is between 0 and 80 percent by weight of the ultimate formulation: a preferred amount is between 5 and 80 percent: and a most preferred amount is between 20 and 40 percent. The amount of mold release agent in the solid compositions of the present invention is between 0 and 10 percent by weight of the ultimate formulation; a preferred amount is between 0 and 5 percent; and a most preferred amount is between 0 and 4 percent.

The preferred antimicrobial compound of the solid composition is 2,2-dibromo-3-nitrilopropionamide. The preferred hydrophilic polymer is hydroxypropyl methylcellulose. Preferred compression agents are lactose and dicalcium phosphate dihydrate. A preferred mold release agent is stearic acid

The solid compositions of the present invention are typically formulated using standard tableting procedures known in the art, e.g., by either wet or dry granulation; therefore, a compression agent and a mold release agent are particularly valuable in such tablet formation procedures. The tablets typically have an ultimate compression density ranging from 0.75 g/cubic centimeter $(cm)^3$ to 1.7 g/cm^3.

The solid composition of the present invention in tablet form can be in a variety of shapes, e.g., cylindrical, oval, or spherical. The size of the tablets will vary over a wide range depending upon the particular application and the particular quantities of ingredients and the only limitation placed on the size of the tablets are the limitations of the production equipment employed. However, it is contemplated that for most applications, tablets will vary in size between 0.1 gram (g) to 10 kilograms (kg); a preferred size is between 1 g and 1 kg. It is preferred that the solid compositions of the present invention are in the form of non-friable, non-dusting, solid tablets.

The compositions of the present invention exhibit sustained release of the antimicrobial compound which leads to an unexpected level of microbiological control of an aqueous industrial system over time. While it is not desired to be bound by any particular theory or mode of action it is believed that when the solid composition of the present invention is contacted with water, that the hydrophilic cellulosic polymer then forms a gel layer on the outside of the composition (e.g. periphery of a tablet). The gel layer then acts as a barrier which prevents further penetration of water into the composition until such time that the gel layer is eroded and replaced with more gel layer (in essence a moving barrier).

In carrying out the methods of the present invention it is contemplated that the solid composition can be placed in a perforated container constructed of a material compatible with said composition, particularly with the antimicrobial compound, such as polyethylene. The container can then be contacted with the industrial water to be treated. This embodiment isolates the active antimicrobial compound from direct contact with metal surfaces which could potentially be corroded by the active antimicrobial compound, and also limits the flow of water over the surface of the composition which allows for an even longer treating time period (i.e., prolonged sustained release).

The tablets in accordance with the present invention can also optionally have an additional thin coating.

The composition of the present invention can optionally contain other inert or active ingredients such as corrosion inhibitors or scale inhibitors.

The present invention is further illustrated by the following examples. All percentages are by weight unless otherwise indicated.

Example I

The method of the present invention was demonstrated in trials in an actual cooling tower system. The method of the present invention was compared to a prior art slug dose method. The cooling tower trials and the results obtained are described below.

Materials and Methods

The cooling system used consisted of a Marley tower (The Marley Cooling Tower Company, Mission, KS) connected through appropriate plumbing to a heat exchanger. The cooling system w s located in Midland, MI. The capacity of the system is 1500 gallons (5.68 m^3) Temperature drop across the tower averages 5.6 °C. The rate of flow in the system is 750 gallons per minute (2.89 m^3/min) with a variable percent of the total flow going over the tower. Typically, the tower operates at 8 cycles of concentration.

The blowdown is controlled by an on-line conductivity meter and make-up water is regulated by a float in the tower basin. Conductivity during the studies varied from a low of approximately 400 microhms to a high of approximately 1250 microhms. Make-up water varied in the range from 9.46-17.03 m^3, (2500-4500 gallons per day. Hardness was measured at least weekly and was typically near 800 ppm.

From May 6, 1986, to June 3, 1986, the biocide treatment in the tower consisted of slug doses of DBNPA. Doses of 3 ppm active ingredient were given 7 days per week by metering a 5 percent solution of DBNPA over a 15 minute period. During this time, weather conditions were also recorded. Average daily high and low temperatures were 16 and 6°C, respectively. Total precipitation during the period was 7.3 cm with a daily range of 0-4.0 cm. On five days per week, samples of water from the system were collected in sterile bottles at a sampling port between the tower and the heat exchanger.

Generally, two samples per day were taken, one immediately prior to DBNPA addition and a second approximately four hours after dosing. Three serial dilutions of the samples were made by adding one milliliter (ml) sample to nine ml of sterile saline. Triplicate 10 microliter inoculations of the samples and dilutions were then made on Trypticase Soy Agar (Difco Laboratories) plates. The plates were incubated for a total of 72 hours at 32°C. At 24 hour intervals, the number of colonies per inoculation were counted (if possible). Organisms per ml of original sample were determined based on the average of the triplicate inoculations. Plate counts read at 24 hours were considered indicative of the fast growing population while 48 and 72 hour counts were considered indicative of the combined fast and slow growers. No attempt was made to classify the organisms.

The tower was treated using timed-release tablets containing DBNPA on two occasions. Tablets weighing approximately 250 grams were prepared and contained 40 percent solid DBNPA, 30 percent Methocel® K15M, 27 percent dicalcium phosphate dihydrate, and 3 percent stearic acid. Tablets were formed under pressure at 20,000 psi (137.9 MPa) and measured about 5 cm in diameter by 8.25 cm in height. The first time the tower was treated, three tablets were placed in a submerged shallow polyethylene tray situated below the tower fill. This was done to provide moderate water movement by the tablets. The total amount of DBNPA in the three tablets was equivalent to 53 parts per million (ppm) based on total volume of the system. This treatment began on August 11, 1986. Following introduction of the tablets, samples were taken five days per week and treated as before. Visual observations of the tablets were also made at the time of each sampling. During the experiment the average daily high and low temperature readings were 26 and 14°C, respectively. Total precipitation was 0.81 cm, with a daily range from 0-0.074 cm. During the weekend of August 23-24, 1986, the fan motor malfunctioned, causing the water in the basin to heat to an estimated 65°C. This caused the tablets to melt prematurely.

Because the system had been disrupted during the first treatment, a second set of three tablets of the same composition and size was introduced on September 2, 1986. Samples and plate counts were performed as before for a total of four weeks. After this time, the sample tray was removed and the residue and remainder of the tablets were analyzed to determine the quantity of DBNPA which remained. During this portion of the experiment the average daily high and low temperatures were 19.5 and 11°C, respectively. Overall precipitation was 48.8 cm (19.21 inches), with a daily range of 0-25.7 cm (0-10.11 inches). At the conclusion of this final study the residue and remainder of the tablets were analyzed to determine whether DBNPA remained. This was done by High Performance Liquid Chromatography (HPLC) following shaking the residue with 500 ml acetonitrile.

Results

Microbiological data compiled during the period from May 6, 1986, to June 3, 1986, are shown in Table 1 as Treatment data. Also included in Table 1 are results from samples taken on three days prior to dosing with DBNPA. Where two samples are shown on the same day, the first sample was taken prior to the daily dose and the second taken approximately four hours after dosing. Generally the samples after dosing show a reduction in the number of colony forming units (CFU's). There is also a trend for the population to rebound, i.e., to be much higher by the following day. This is presumably due to the total degradation of DBNPA in a relatively short period of time (as well as loss in the blowdown). The half-life of DBNPA in this tower was determined to be very short, estimated at less than one hour. The plate count data was highly variable. The total dose of DBNPA given to the system during this time was 99 ppm, based on tower volume.

On August 11, 1986 three timed-release tablets containing a total of 300 g DBNPA were used to treat the tower. This is equivalent to a total dose of 53 ppm DBNPA. The tablets were placed in a shallow polyethylene tray which was submerged in the water directly below the fill. Slight water movement could be felt above the tray. Plate count data from samples taken before (pre-treatment data) and during (treatment

data) treatment are given in Table 2. As these data show, the numbers of both fast and slow growing organisms were substantially lower during this phase of the experiment. This is true whether the comparison is made to the counts immediately prior to treatment (when no biocide was used) or to the counts obtained when treating the tower with daily slug doses of 3 ppm DBNPA.

During sampling on August 25th, it was noted that the fan was not operating and the entire volume of water in the system was hot. It was learned that the fan motor had malfunctioned sometime between August 23rd and 25th. As a result of the heating, the tablets melted and only a small residue remained (note that a visual examination of the tablets on August 22nd was made and an estimated half of the original tablet appeared to be intact). The residue was presumed due to the water-insoluble dicalcium phosphate dihydrate in the tablet. The tray and residue were removed from the tower on August 26th. Plate counts from samples taken August 25th and 26th indicated the tower to be essentially sterile (likely due to either the heat or the release of the remaining DBNPA).

Pre-treatment samples were taken again between August 27th and September 2nd and the tower was shown to be contaminated as would be expected with no biocide treatment. On September 2nd, three new tablets were placed in the tower in a manner similar to before. Subsequently, samples were taken five days per week and plate counts performed. The results of these pre-treatment and treatment data are given in Table 3. At the conclusion of this study, the amount of DBNPA which remained was measured by HPLC and found to be approximately 4.5 grams, i.e. about 1.5 percent of the total original dose.

Based on the mean plate count data and the known or estimated total dose to the tower, the relative effectiveness of slug dosing vs. continuous dosing with timed-release tablets was calculated. The dose for the first tablet trial was estimated based on the fact that during the second trial similar tablets appeared to retain activity for approximately 21 days. Since accurate measurements could only be made during the first 11 days of the first tablet trial, the dose was estimated at 28 ppm DBNPA for the 11 day period, assuming that the overall release of DBNPA is linear.

The factors by which the planktonic plate counts were reduced, normalized for the difference in overall dose of DBNPA, were used to determine the relative biocidal activity. The relative effectiveness was shown to increase during use of the timed-release tablets by a factor of between 8 and 99 times. These data are summarized in Table 4. In general, it also appears that the increase in effectiveness is greater for faster growing organisms than for slower species. The data from 24 hour plate counts indicates that the potency increases by a factor of 33 to 99, whereas the same data for the slower growing population showed increased potency factor of 8 to 29.

These data do not take into account the ambient weather conditions in the calculation of effectiveness increase. Theoretically, a higher ambient temperature will cause an increased load on the tower and will result in a greater microbiological problem. If that is true, then the increase in effectiveness for timed-release tablets could be greater than these data indicate.

Tabl 1
Cooling Tower Treated with 3ppm DBNPA/day, 7 Days per Week; Plate Count Summary

Date	24 hr Count	48 hr Count	72 hr Count
04/29	780,000*		2,300,000
04/30	230,000		830,000
05/01			1,900,000
Pre-treatment data			
Treatment data			
05/02			17,000
05/05	2,700	84,000	220,000
05/06	320,000	390,000	390,000
05/06	290,000		
05/07	230,000	2,500,000	2,500,000
05/07	69,000	73,000	73,000
05/08	460,000	270,000	
05/08	29,000	120,000	
05/09	1,700,000	1,700,000	1,700,000
05/09	19,000	67,000	93,000
05/12	820,000	1,800,000	1,900,000
05/12	56,000	310,000	350,000
05/13	520,000	2,000,000	2,000,000
05/13	9,700	160,000	190,000
05/14	170,000	560,000	870,000
05/16	120,000	240,000	240,000
05/16	88,000	150,000	150,000
05/19	480,000	530,000	550,000
05/19	260,000	270,000	300,000
05/20	150,000	260,000	260,000
Mean (Treatment Data)	199,771	596,865	679,000

*Numbers refer to colony forming units

Table 1 continued

Date	24 hr Count	48 hr Count	72 hr Count
05/20	1,500	43,000	44,000
05/21	120,000	600,000	650,000
05/21	1,800	44,000	67,000
05/22	190,000	2,900,000	2,900,000
05/22	24,000	200,000	220,000
05/23	400,000	1,200,000	1,600,000
05/23	19,000	93,000	220,000
05/27	29,000	710,000	1,200,000
05/27	24,000	470,000	570,000
05/28	200,000	510,000	900,000
05/28	130,000	400,000	750,000
05/29	88,000	260,000	870,000
05/29	51,000	470,000	660,000
05/30	41,000	340,000	1,400,000
05/30	30,000	310,000	1,100,000
06/02	20,000	110,000	850,000
06/02	9,600	170,000	270,000
06/03	340,000	720,000	930,000
06/03	79,000	600,000	680,000
Mean (Treatment Data)	199,771	596,865	679,000

*Numbers refer to colony forming units

Tabl 2

Cooling Tower Treated with 3 Timed-Released DBNPA Tablets Plate Count Summary (Total Dose Equals 53 ppm)

Date	24 hr Count	48 hr Count	72 hr Count
08/05	29,000*	1,100,000	1,200,000
08/05	38,000	1,100,000	1,400,000
08/06	36,000	980,000	1,000,000
08/06	35,000	1,000,000	1,000,000
08/07	12,000		
08/07	17,000		
08/11	19,000	110,000	140,000
Pre-treatment data			
Treatment data			
08/12	11,000	. 120,000	200,000
08/13	6,000	140,000	170,000
08/14	4,300	32,000	60,000
08/14	4,300	55,000	100,000
08/15	4,000	48,000	52,000
08/15	3,700	33,000	42,000
08/18	15,000	93,000	100,000
08/19	7,800	53,000	58,000
08/20	4,800	63,000	98,000
08/21	8,700	97,000	130,000
08/22	8,700	72,000	100,000

Fan stopped on weekend of 8/23-8/24. Water got hot. Tablets melted. Plate counts after cessation of treatment showed tower became heavily contaminated.

Mean	7,118	73,273	100,909

(Treatment Data)

*Numbers refer to colony forming units.

Table 3
Cooling Tower Treated with 3 Timed-Released DBNPA Tablets Plate Count Summary (Total Dose Equals 53 ppm)

Date	24 hr Count	48 hr Count	72 hr Count
08/27	98,000*	700,000	
08/28	720,000	1,000,000	
08/29	52,000	60,000	
09/02	48,000	330,000	600,000
	Pre-treatment data		
	Treatment data		
09/03	10,000	75,000	250,000
09/04	17,000	110,000	380,000
09/05	5,700	11,000	87,000
09/08	11,000	68,000	75,000
09/09	5,000	55,000	770,000
09/10	9,700	72,000	280,000
09/11	22,000	55,000	180,000
09/12	13,000	50,000	83,000
09/15	15,000	35,000	
09/16	<50**	<50**	1,200**
09/18	14,300	45,000	100,000
09/19	4,500	52,000	130,000
09/22	7,500	18,000	22,000
09/23	25,000	88,000	170,000
09/24	80,000	200,000	350,000
09/25	95,000	420,000	
09/26	130,000	140,000	
09/29	13,000		
Mean (Treatment Data)	11,411	53,733	183,086

*Numbers refer to colony forming units
**Due to weather conditions, flow over tower was discontinued and sample for this count was taken from the basin.

Table 4

Comparison of plate counts taken during intermittent dosing and dosing with DBNPA containing tablets.

Note: Total dose during intermittent dosing was 3 ppm/day X 33 days = 99 ppm DBNPA.
Total estimated dose from first tablet trial = 28 ppm DBNPA, based on the fact that 11 days elapsed and that the 53 ppm tablet has been observed to remain effective for 21 days.
Total dose from the second tablet trial = 53 ppm.

---

24 Hour Data:

Mean for intermittent dosing = 199,771 CFU/ml
Mean for first tablet trial = 7,118 CFU/ml
Effectiveness increased by 99 times.*
Mean for second tablet trial = 11,411 CFU/ml
Effectiveness increased by 33 times.*

---

48 Hour Data:

Mean for intermittent dosing = 596,865 CFU/ml
Mean for first tablet trial = 73,273 CFU/ml
Effectiveness increased by 29 times.*
Mean for second tablet trial = 53,773 CFU/ml
Effectiveness increased by 21 times.*

---

72 Hour Data:

Mean for intermittent dosing = 769,000 CFU/ml
Mean for first tablet trial = 100,909 CFU/ml
Effectiveness increased by 27 times.*
Mean for second tablet trial = 183,086 CFU/ml
Effectiveness increased by 8 times.*

---

*The increase in effectiveness was calculated based on the difference in mean plate counts and difference in total dose, as follows:

$$\frac{\text{PC (tablets)}}{\text{PC (slug)}} \times \frac{\text{Total dose (slug)}}{\text{Total dose (tablet)}} = \text{Increase Factor},$$

where PC = mean plate count, i.e., mean number of organisms based on the number of colony forming units.

Claims

1. A solid antimicrobial composition comprising:
(a) 1 to 90 percent by weight of a halogenated amide antimicrobial compound of the formula,

$$R^1-\overset{\overset{Br}{|}}{\underset{\underset{X}{|}}{C}}-\overset{\overset{O}{\|}}{C}-N-(R)_2$$

wherein
X is hydrogen, halogen or a cyano radical;
each R group is independently hydrogen, a monovalent saturated hydrocarbon radical or an inertly substituted monovalent saturated hydrocarbon radical or the two R groups are, jointly, a divalent saturated hydrocarbon radical, or an inertly substituted divalent saturated hydrocarbon radical, which, taken with the adjacent nitrogen atom, forms a heterocyclic ring having from 4 to 10 ring members; and
R^1 is a cyano radical or an amido radical having the formula:

$$-\overset{\overset{O}{\|}}{C}-N-(R^2)_2$$

wherein R^2 has the same meaning as R;
(b) 10 to 80 percent by weight of a suitable hydrophilic polymer which is a natural water soluble cellulosic polymer, a synthetic water soluble cellulosic polymer, gelatin, maltodextrin, xanthan gum, carrageenan, carboxymethyl guar, hydroxypropyl guar, carboxymethyl galactomannose or poly-vinylpyrrolidone;
(c) 0 to 80 percent by weight of a compression agent; and
(d) 0 to 10 percent by weight of a mold release agent.

2. The composition of claim 1 comprising:
(a) 10 to 50 percent by weight of the halogenated amide antimicrobial compound,
(b) 20 to 50 percent by weight of the hydrophilic polymer,
(c) 5 to 80 percent by weight of a compression agent, and
(d) 0 to 5 percent by weight of a mold release agent.

3. The composition of claim 2 comprising:

(a) 30 to 50 percent by weight of the halogenated amide antimicrobial compound,
(b) 20 to 40 percent by weight of the hydrophilic polymer,
(c) 20 to 40 percent by weight of a compression agent, and
(d) 0 to 4 percent by weight of a mold release agent.

4. The composition of claim 1 wherein X is hydrogen, chlorine or bromine, R^1 is cyano, and each R is independently hodrogen, lower alkyl or phenyl.

5. The composition of claim 4 wherein X is hydrogen or bromine, R^1 is cyano, and each R is independently hydrogen or methyl.

6. The composition of any one of claims 1 to 3 wherein the halogenated amide antimicrobial compound is 2-bromo-3-nitrilopropionamide, 2-bromo-2,3-dinitrilopropionamide, 2,2-dibromo-3-nitrilopropionamide, N-(n-butyl)-2-bromo-3-nitrilopropionamide; N,N-dimethyl-2,2-dibromo-3-nitrilopropionamide, 2-chloro-2-bromo-3-nitrilopropionamide, N-(n-propyl)-2-iodo-2-bromo-3-nitrilopropionamide, N-methyl-N-ethyl-2-fluoro-2-bromo-3-nitrilopropoinamide, N-phenyl-2-cyano-2-bromo-3-nitrilopropionamide, N-cyclohexyl-2,2-dibromo-3-nitrilopropionamide, N-benzyl-2-bromo-3-nitrilopropionamide, N-(2,2-dibromo-3-nitrilopropionoyl)-piperdine, 2-bromomalonic diamide, 2-2-dibromomalonic diamide, N-methyl-N'-ethyl-2-chloro-2-bromomalonic diamide, N-Phenyl-2-iodo-2-bromomalonic diamide, N-methyl-2-bromo-3-nitrilopropionamide, N-phenyl-2-bromo-2-chloro-3-nitrilopropionamide, N-methyl-2,2-dibromo-3-nitrilopropionamide, N,N-dimethyl-2-bromo-3-nitrilopropionamide, N,N-diethyl-2,2-dibromo-3-nitrilopropionamide, N-(n-butyl)-2,2-dibromo-3-nitrilopropionamide, or N-phenyl-N-methyl-2,2-dibromo-3-nitrilopropionamide.

7. The composition of any one of claims 1 to 5 wherein the halogenated amide antimicrobial compound is 2,2-dibromo-3-nitrilopropionamide.

8. The composition of any one of claims 1 to 7 wherein the hydrophilic polymer is methyl cellulose or hydroxypropyl methyl cellulose.

9. The composition of any one of claims 1 to 8 wherein the compression agent is lactose and the mold release agent is stearic acid.

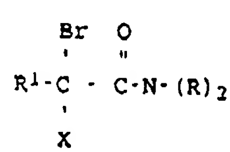
10. The composition of claim 9 wherein the halogenated amide antimicrobial compound is 2,2-dibromo-3-nitrilopropionamide, the hydrophilic polymer is hydroxypropylmethyl cellulose, the compression agent is lactose, and the mold release agent is stearic acid.

11. A method for biological control in an aqueous industrial system comprising contacting the system with an antimicrobially effective amount of the solid antimicrobial composition of any one of claims 1 to 10.

12. The method of claim 11 wherein the aqueous industrial system is a cooling tower, metalworking fluid, pulp and paper system, or air washer.

Patentansprüche

1. Eine feste antimikrobielle Zusammensetzung umfassend:
   (a) 1 bis 90 Gew.-% einer antimikrobiellen halogenierten Amidverbindung der Formel



worin
X Wasserstoff, Halogen oder ein Cyanrest ist;

jede Gruppe R unabhängig Wasserstoff, ein einwertiger gesättigter Kohlenwasserstoffrest oder ein inert substituierter einwertiger gesättigter Kohlenwasserstoffrest ist oder die beiden Gruppen R zusammen ein zweiwertiger gesättigter Kohlenwasserstoffrest oder ein zweiwertiger inert substituierter gesättigter Kohlenwasserstoffrest sind der zusammen mit dem benachbarten Stickstoffatom einen heterocyclischen Ring mit 4 bis 10 Ringgliedern bildet; und
R^1 ein Cyanrest oder ein Amidrest ist mit der Formel

$$-\overset{\overset{\displaystyle O}{\|}}{C}-N\!\left(R^2\right)_2$$

worin R^2 die gleiche Bedeutung wie R hat;
(b) 10 bis 80 Gew.-% eines geeigneten hydrophilen Polymers das ein natürliches, wasserlösliches Cellulosepolymer, ein synthetisches, wasserlösliches Cellulosepolymer, Gelatine, Maltodextrin, Xanthangummi, Karrageen, Carboxymethylguar, Hydroxypropylguar, Carboxymethylgalactomannose oder Polyvinylpyrrolidon ist;
(c) 0 bis 80 Gew.-% eines Verdichtungsmittels; und
(d) 0 bis 10 Gew.-% eines Formtrennmittels.

2. Die Zusammensetzung nach Anspruch 1 umfassend:
(a) 10 bis 50 Gew.-% der antimikrobiellen halogenierten Amidverbindung;
(b) 20 bis 50 Gew.-% des hydrophilen Polymers;
(c) 5 bis 80 Gew.-% eines Verdichtungsmittels, und
(d) 0 bis 5 Gew.-% eines Formtrennmittels.

3. Die Zusammensetzung nach Anspruch 2 umfassend:
(a) 30 bis 50 Gew.-% der antimikrobiellen halogenierten Amidverbindung,
(b) 20 bis 40 Gew.-% des hydrophilen Polymers,
(c) 20 bis 40 Gew.-% eines Verdichtungsmittels, und
(d) 0 bis 4 Gew.-% eines Formtrennmittels.

4. Die Zusammensetzung nach Anspruch 1, worin X Wasserstoff, Chlor oder Brom ist, R^1 Cyan ist und jedes R unabhängig Wasserstoff, niedriges Alkyl oder Phenyl ist.

5. Die Zusammensetzung nach Anspruch 4, worin X Wasserstoff oder Brom ist, R^1 Cyan ist und jedes R unabhängig Wasserstoff oder Methyl ist.

6. Die Zusammensetzung nach einem der Ansprüche 1 bis 3, worin die antimikrobielle halogenierte Amidverbindung 2-Brom-3-nitrilpropionamid, 2-Brom-2,3-dinitrilpropionamid, 2,2-Dibrom-3-nitrilpropionamid, N-(n-butyl)-2-brom-3-nitrilpropionamid; N,N-Dimethyl-2,2-dibrom-3-nitrilpropionamid, 2-Chlor-2-brom-3-nitrilpropionamid, N-(n-propyl)-2-jod-2-brom-3-nitrilpropionamid, N-Methyl-N-ethyl-2-fluor-2-brom-3-nitrilpropionamid, N-Phenyl-2-cyan-2-brom-3-nitrilpropionamid, N-Cyclohexyl-2,2-dibrom-3-nitrilpropionamid, N-Benzyl-2-brom-3-nitrilpropionamid, N-(2,2-dibrom-3-nitrilpropionoyl)-piperidin, 2-Brommalondiamid, 2,2-Dibrommalondiamid, N-Methyl-N'-ethyl-2-chlor-2-brommalondiamid, N-Phenyl-2-jod-2-brommalondiamid, N-Methyl-2-brom-3-nitrilpropionamid, N-Phenyl-2-brom-2-chlor-3-nitrilpropionamid, N-Methyl-2,2-dibrom-3-nitrilpropionamid, N,N-Dimethyl-2-brom-3-nitrilpropionamid, N,N-Diethyl-2,2-dibrom-3-nitrilpropionamid, N-(n-butyl)-2,2-dibrom-3-nitrilpropionamid, oder N-Phenyl-N-methyl-2,2-dibrom-3-nitrilpropionamid ist.

7. Die Zusammensetzung nach einem der Ansprüche 1 bis 5, worin die antimikrobielle halogenierte Amidverbindung 2,2-Dibrom-3-nitrilpropionamid ist.

8. Die Zusammensetzung nach einem der Ansprüche 1 bis 7, worin das hydrophile Polymer Methylcellulose oder Hydroxypropylmethylcellulose ist.

9. Die Zusammensetzung nach einem der Ansprüche 1 bis 8, worin das Verdichtungsmittel Lactose und das Formtrennmittel Stearinsäure ist.

10. Die Zusammensetzung nach Anspruch 9, worin die antimikrobielle halogenierte Amidverbindung 2,2-dibrom-3-nitrilpropionamid ist, das hydrophile Polymer Hydroxypropylmethylcellulose ist, das Verdichtungsmittel Lactose ist und das Formtrennmittel Stearinsäure ist.

11. Methode zur biologischen Kontrolle in einem wäßrigen industriellen System umfassend das Kontaktieren des Systems mit einer antimikrobiell wirksamen Menge der festen antimikrobiellen Zusammensetzung nach einem der Ansprüche 1 bis 10.

12. Die Methode nach Anspruch 11, worin das wäßrige industrielle System ein Kühlturm, ein Metallverarbeitungsfluid, ein Pulpe- und Papiersystem oder ein Luftwascher ist.

Revendications

1. Composition antimicrobienne solide, comprenant :

a) 1 à 90% en poids d'un composé antimicrobien amide halogéné de formule

$$R^1-\overset{\overset{\displaystyle Br}{|}}{\underset{\underset{\displaystyle X}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-N-(R)_2$$

dans laquelle

X est un atome d'hydrogène ou d'halogène ou un radical cyano;

chaque groupe R est indépendamment un atome d'hydrogène, un radical hydrocarboné saturé monovalent ou un radical hydrocarboné saturé monovalent portant un substituant inerte, ou bien les deux groupes R sont, ensemble, un radical hydrocarboné saturé divalent ou un radical hydrocarboné saturé divalent portant un radical inerte formant, avec l'atome d'azote adjacent, un noyau hétérocyclique comportant de 4 à 10 chaînons; et

R^1 est un radical cyano ou un radical amido de formule :

$$-\overset{\overset{\displaystyle O}{\|}}{C}-N(R^2)_2$$

dans laquelle R^2 a la même signification que R;

(b) 10 à 80% en poids d'un polymère hydrophile convenable, qui est un polymère cellulosique naturel hydrosoluble, un polymère cellulosique synthétique hydrosoluble, de la gélatine, de la maltodextrine, de la gomme xanthane, de la carragénine, du carboxyméthyl-guar, de l'hydroxypropyl-guar, du carboxyméthylgalactomannose ou de la polyvinylpyrrolidone;

(c) 0 à 80% en poids d'un agent de compression; et

(d) 0 à 10% en poids d'un agent de démoulage.

2. Composition selon la revendication 1, comprenant :

(a) 10 à 50% en poids du composé antimicrobien amide halogéné,

(b) 20 à 50% en poids du polymère hydrophile,

(c) 5 à 80% en poids d'un agent de compression, et

(d) 0 à 5% en poids d'un agent de démoulage.

3. Composition selon la revendication 2, comprenant :

(a) 30 à 50% en poids du composé antimicrobien amide halogéné,

(b) 20 à 40% en poids du polymère hydrophile,

(c) 20 à 40% en poids d'un agent de compression, et
(d) 0 à 4% en poids d'un agent de démoulage.

4. Composition selon la revendication 1, dans laquelle X est un atome d'hydrogène, de chlore ou de brome, R^1 est un radical cyano et chaque R est indépendamment un atome d'hydrogène ou un radical alkyle inférieur ou phényle.

5. Composition selon la revendication 4, dans laquelle X est un atome d'hydrogène ou de brome, R^1 est un radical cyano et chaque R est indépendamment un atome d'hydrogène ou un radical méthyle.

6. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle le composé antimicrobien amide halogéné est le 2-bromo-3-nitrilopropionamide, le 2-bromo-2,3-dinitrilopropionamide, le 2,2-dibromo-3-nitrilopropionamide, le N-(n-butyl)-2-bromo-3-nitrilopropionamide, le N,N-diméthyl-2,2-dibromo-3-nitrilopropionamide, le 2-chloro-2-bromo-3-nitrilopropionamide, le N-(n-propyl)-2-iodo-2-bromo-3-nitrilopropionamide, le N-méthyl-N-éthyl-2-fluoro-2-bromo-3-nitrilopropionamide, le N-phényl-2-cyano-2-bromo-3-nitrilopropionamide, le N-cyclohexyl-2,2-dibromo-3-nitrilopropionamide, le N-benzyl-2-bromo-3-nitrilopropionamide, la N-(2,2-dibromo-3-nitrilopropionoyl)pipéridine, le diamide 2-bromomalonique, le diamide 2,2-dibromomalonique, le diamide N-méthyl-N'-éthyl-2-chloro-2-bromomalonique, le diamide N-phényl-2-iodo-2-bromomalonique, le N-méthyl-2-bromo-3-nitrilopropionamide, le N-phényl-2-bromo-2-chloro-3-nitrilopropionamide, le N-méthyl-2,2-dibromo-3-nitrilopropionamide, le N,N-diméthyl-2-bromo-3-nitrilopropionamide, le N,N-diéthyl-2,2-dibromo-3-nitrilopropionamide, le N-(n-butyl)-2,2-dibromo-3-nitrilopropionamide ou le N-phényl-N-méthyl-2,2-dibromo-3-nitrilopropionamide.

7. Composition selon l'une quelconque des revendications 1 à 5, dans laquelle le composé antimicrobien amide halogéné est le 2,2-dibromo-3-nitrilopropionamide.

8. Composition selon l'une quelconque des revendications 1 à 7, dans laquelle le polymère hydrophile est la méthylcellulose ou l'hydroxypropylméthylcellulose.

9. Composition selon l'une quelconque des revendications 1 à 8, dans laquelle l'agent de compression est le lactose et l'agent de démoulage est l'acide stéarique.

10. Composition selon la revendication 9, dans laquelle le composé antimicrobien amide halogéné est le 2,2-dibromo-3-nitrilopropionamide, le polymère hydrophile est l'hydroxypropylméthylcellulose, l'agent de compression est le lactose et l'agent de démoulage est l'acide stéarique.

11. Procédé de traitement biologique d'un système aqueux industriel, comprenant la mise en contact du système avec une quantité antimicrobienne efficace de la composition antimicrobienne solide selon l'une quelconque des revendications 1 à 10.

12. Procédé selon la revendication 11, dans lequel le système aqueux industriel est une tour de refroidissement, un fluide métallurgique, un système de pâte et de papier ou un humidificateur d'air.